

## I. The Claims Are Patentable over the Cited References

Applicants respectfully disagree with the rejection of claims 1-7, 11-14 and 17-23. The applied references do not disclose a medicinal aerosol solution formulation comprising an active ingredient subject to a degradation by means of peroxides or other leachables as recited in claim 1.

The technical problem underlying the present invention is to provide an aerosol solution formulation product with improved chemical stability of a certain kind of active ingredients for use in connection with a pressurized metered dose inhaler. The technical problem underlying the present invention is related to the finding by the present inventors that peroxides released from the rubber materials used as valve gasket or other compounds that can leach from the closure system into the formulation affect the chemical stability of certain active ingredients (steroids in particular) in solution formulations comprising a HFA propellant and a co-solvent).

The problem can be worsened by standard metered dose inhaler canisters having a cutting edge opening. The cutting edge, during the valve printing phase, may lead to a damage and compression of the surface of the rubber, which may cause breaks or cuts in the rubber materials used as valve gaskets and consequent release of peroxides and leachables with time in the solution formulation.

The offered solution is a canister provided with a rim with rounded edges which avoids contact of a sharp edge with rubber materials used as valve gaskets.

No document of the cited references deals with the above-mentioned technical problem or provide evidence that breaks which can occur in the rubber materials facilitate the release of peroxides and other leachables into the medicinal solution and that that peroxides and leachables impair the chemical stability of active ingredients in a formulation comprising a HFA propellant, a co-solvent and optionally a low-volatility component, stored in aerosol canisters equipped with a metering valve.

Jager relates to stabilized medicinal aerosol solution formulations comprising medicaments that degrade or decompose by **interaction with solvents or water**, a HFC propellant, a co-solvent and an acid. Furthermore, specific medicinal aerosol solution formulations comprising ipratropium bromide or fenoterol, ethyl alcohol, 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3-heptafluoropropane, and either an inorganic acid or an organic

acid are described. The acids are present in amounts sufficient to reduce the degradation of the medicaments to acceptable levels; cf. abstract of Jager.

The degradation or decomposition of the medicament must be acid sensitive in that the rate of degradation or decomposition can be effectively reduced by the addition of acid; cf. column 3, lines 44-47 of Jager.

The present invention relates to medicinal aerosol solution formulation products, the medicinal aerosol solution formulation comprising an active ingredient subject to a degradation by means of peroxides and/or other leachables, i.e. compounds that can leach from elastomeric or plastic components and the closure system, and in particular from the rubber materials used as valve gasket, as a result of direct contact with the formulation contained in the aerosol canister.

According to pending claim 8, the active ingredient is a corticosteroid and according to claim 9, the corticosteroid is a 20-ketosteroid. The 20-ketosteroid is selected from the group consisting of budesonide and its epimers, mometasone furoate, triamcinolone acetonide, butixocort and ciclesonide; cf. claim 10.

Thus, Jager does not teach the features of the present invention in that the medicaments referred to in the cited references degrade or decompose by interaction with solvents or water rather than by means of peroxides and/or other leachables as it is the case in the present invention. Moreover, the class and type of medicaments recited in this cited reference, i.e. ipratropium bromide and fenoterol differ from the kind of medicaments recited in the present invention as being subject to a degradation by means of peroxides and/or other leachables. Finally, according to Jager ipratropium bromide and fenoterol are stabilized against the degradation by interaction with solvents or water by adding acids, i.e. by adapting the aerosol solution formulation rather than the aerosol canister containing the medicinal aerosol solution formulation as it is the case according to the present invention.

Accordingly, Jager fails to teach the features of the present invention. The only common feature is the aim to stabilize a medicinal aerosol solution formulation. However, as mentioned before, the kind of medicaments is different and the solution of the technical problem is different in that according to the applied references the medicaments are stabilized by way of a further additive in the aerosol solution formulation, whereas according to the present invention the aerosol canister has been adapted such that a stabilization can be obtained.

Therefore, there was no motivation at all for a person skilled in the art to combine Jager with Lasserre in order to find a solution to the technical problem underlying the present invention.

Lasserre does not provide any hint whatsoever to change the type of medicament recited in Jager and not to use acids as an additive in the aerosol solution formulations and to amend the aerosol canister instead, in order to arrive at the teaching underlying the present invention.

Lasserre relates to a mounting device for mounting a valve on a container containing a product that is to be dispensed with the add of a pressurized gas, and to a dispenser equipped with such a device. More specifically, this applied reference is aimed at improving dispensers commonly known as “aerosol dispensers”; cf. column 1, lines 9-14.

One object consists in providing a leaktight and reliable mounting of a valve on any kind of container, using means which are simple and easy to implement, and to do so in particular for containers with wide manufacturing tolerances; cf. column 2, lines 39-43.

Thus, this applied reference is not at all concerned with the problem of stabilizing active ingredients in medicinal aerosol solution formulations.

Furthermore, this applied reference discloses the use of dispensers of the “aerosol” type for packaging and dispensing products in various fields, such as the field of cosmetics, dermopharmaceutical, household or food, in the field of paint, health and hygiene, in the field of technical products, adhesives, insecticides, plant-treatment products, etc.; column 1, lines 15-20.

Thus, this applied reference does not relate to medicinal aerosol solution formulations for pressurized metered dose inhalers for the inhalation of active ingredients.

Again, the invention underlying Lasserre does not relate to the subject-matter and technical problem underlying the present invention. In addition, it does not provide any hint whatsoever for a person skilled in the art to solve the technical problem underlying the present invention as outlined above.

Actually, a person skilled in the art would not take this document into consideration when looking for a solution of the technical problem underlying the present invention.

Applicants respectfully disagree with the rejection of claims 8-10 and 15-16. Applicants respectfully disagree with the rejection of claims 8-10 and 15-16 for at least the reasons stated above with respect to claim 1-7, 11-14 and 17-23 and the following additional reasons.

Britto refers to a metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

It has been found that coating the interior can surfaces of MDIs with a fluorocarbon polymer significantly reduces or essentially limits the problem of **drug adhesion or deposition on the can walls** and thus ensures consistent delivery of medication in aerosol form from the MDI **where the active ingredient is suspended in the formulation.**

Thus, Britto deals with the technical problem of the adhesion of the drug present as a suspension in the formulation to the inner surfaces of the can (i.e. walls, valves and cans).

Furthermore, aerosol canisters provided with rollover rims etc. are not described.

In summary, as mentioned above, this applied reference does not provide any hint to the claimed solution to the technical problem underlying the present invention.

As a result, Applicants respectfully submit that there is no motivation taught or suggested by the applied references to modify the teachings of Jager with the teachings of Lasserre and/or Britto to obtain the claimed product. Applicants submit that only through hindsight would one be motivated to modify Jager to meet the features of the claims. MPEP §2141, under the heading “Basic Considerations Which Apply to Obviousness Rejections,” points out that “the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.” *See Hodosh v. Block Drug Co.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). The Federal Circuit has clearly held that “the motivation to combine references cannot come from the invention itself.” *Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 30 USPQ2d 1377 (Fed. Cir. 1993).

Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) should be withdrawn.

## II. The Claims Are Patentable over the Co-Pending Applications

The Office Action provisionally rejects claims 1-16 over the claims of co-pending Application No. 10/290,225. The Applicants respectfully assert that the provisional rejection is improper.

The Office Actions asserts that both the claims of the present application and the claims of the co-pending application include “a solution formulation comprising an active agent, a co-solvent, optionally a low volatility agent.” The provisional rejection is based solely on a portion of the solutions being the same, but fails to compare any of the other features recited in the applications. For example, the Office Action refers to Lasserre to show a teaching of an aluminum canister for aerosol devices with a rolled neck. Pointing to one feature of a canister from a third reference in not a proper comparison of the claims.

Accordingly, the Office Action fails to provide a proper basis for the provisional rejection.

In addition, the Office Action provisionally rejects claims 1-16 over the claims of co-pending Application No. 10/244,519. The claims of the co-pending application have been amended. The Applicants respectfully assert that the claims of the co-pending application contain a different formulation than the formulation in the claims of the present application. For at least this reason, the Applicants respectfully assert that the provisional rejection should be withdrawn.

### III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1-23 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number set forth below.

DATED this 21<sup>st</sup> day of December, 2004

Respectfully submitted,



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